Development of Single Cell MRI Technology using Genetically-Encoded Iron-Based Reporters

Grant Award Details

Development of Single Cell MRI Technology using Genetically-Encoded Iron-Based Reporters

Grant Type: Tools and Technologies II

Grant Number: RT2-02018

Project Objective: The overall project is to develop a new form of cellular MRI by expressing bacterial iron-binding proteins in stem cells, thereby making them endogenously MRI-active. This method would potentially enable single cell detection sensitivity.

Investigator:

Name:	Brian Rutt
Institution:	Stanford University
Type:	PI

Disease Focus: Neurological Disorders, Stroke

Human Stem Cell Use: Adult Stem Cell

Award Value: $1,833,348

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Reporting Period: Year 4/NCE

View Report

Grant Application Details

Application Title: Development of Single Cell MRI Technology using Genetically-Encoded Iron-Based Reporters

Public Abstract:

Clinical application of cell transplantation therapy requires a means of non-invasively monitoring these cells in the patient. Several imaging modalities, including MRI, bioluminescence imaging, and positron emission tomography have been used to track stem cells in vivo. For MR imaging, cells are pre-loaded with molecules or particles that substantially alter the image brightness; the most common such labelling strategy employs iron oxide particles. Several studies have shown the ability of MRI to longitudinally track transplanted iron-labeled cells in different animal models, including stroke and cancer. But there are drawbacks to this kind of labeling. Division of cells will result in the dilution of particles and loss of signal. False signal can be detected from dying cells or if the cells of interest are ingested by other cells.

To overcome these roadblocks in the drive toward clinical implementation of stem cell tracking, it is now believed that a genetic labeling approach will be necessary, whereby specific protein expression causes the formation of suitable contrast agents. Such endogenous and persistent generation of cellular contrast would be particularly valuable to the field of stem cell therapy, where the homing ability of transplanted stem cells, long-term viability, and capacity for differentiation are all known to strongly influence therapeutic outcomes. However, genetic labeling or "gene reporter" strategies that permit sensitive detection of rare cells, non-invasively and deep in tissue, have not yet been developed. This is therefore the translational bottleneck that we propose to address in this grant, through the development and validation of a novel high-sensitivity MRI gene reporter technology.

There have been recent reports of gene-mediated cellular production of magnetic iron-oxide nanoparticles of the same composition as the synthetic iron oxide particles used widely in exogenous labeling studies. It is an extension of this strategy, combined with our own strengths in developing high-sensitivity MRI technology, that we propose to apply to the task of single cell tracking of metastatic cancer cells and neural stem cells.

If we are successful with the proposed studies, we will have substantially advanced the field of in vivo cellular imaging, by providing a stable cell tracking technology that could be used to study events occurring at arbitrary depth in tissue (unlike optical methods) and over unlimited time duration and arbitrary number of cell divisions (unlike conventional cellular MRI).
With the ability to track not only the fate (migration, homing and proliferation) but also the viability and function of very small numbers of stem cells will come new knowledge of the behavior of these cells in a far more relevant micro-environment compared with current in vitro models, and yet with far better visualization and cell detection sensitivity compared with other in vivo imaging methods.

Statement of Benefit to California:

Stem cell therapy has enormous promise to become a viable therapy for a range of illnesses, including stroke, other cardiovascular diseases, and neurological diseases. Progress in the development of these therapies depends on the ability to monitor cell delivery, migration and therapeutic action at the disease site, using imaging and other non-invasive technologies. If breakthroughs could be made along these lines, it would not only be of enormous benefit to the citizens of the state of California, but would also greatly reduce healthcare costs.

From a broader research perspective, the state of California is the front-runner in stem cell research, having gathered not only private investments, as demonstrated by the numerous biotechnology companies that are developing innovative tools, but also extensive public funds that allows the state, through CIRM, to sponsor stem cell research in public and private institutions. In order to preserve the leadership position and encourage research on stem cells, CIRM is calling for research proposals to develop innovative tools and technologies that will overcome current roadblocks in translational stem cell research. This proposal will benefit the state by providing important new technology that will be valuable for both basic and translational stem cell research.

A key bottleneck to the further development and translation of new stem cell therapies is the inability to track stem cells through a human body. It is possible to image stem cells using embedded optical fluorescence labels, but optical imaging does not permit tracking of cells deep in tissue. Other imaging modalities and their associated cellular labels (for example positron emission tomography) have also been used to track cells but do not have the sensitivity to detect rare or single cells. Finally, MRI has been used to track cells deep in tissue, down to the single cell level, but only by pre-loading cells with a non-renewable supply of iron oxide nanoparticles, which prevents long-term tracking and assessment of cell viability and function. We propose here to develop MRI technology and a new form of genetically-encoded, long-term cell labeling technology, to a much more advanced state than available at present. This will make it possible to use MRI to detect and follow cancer and stem cells as they migrate to and proliferate at the site of interest, even starting from the single cell stage. This will provide a technology that will help stem cell researchers, first and foremost in California, to understand stem cell behavior in a realistic in vivo environment. This technology will be translatable to future human stem cell research studies.
